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EXAMINER	
ROYDS, LESLIE A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,016	FIKSTAD ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2008 and 14 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,13-15,20-24,29-33,38,39 and 44-65* is/are pending in the application.

4a) Of the above claim(s) *44-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,13-15,20-24,29-33,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-2, 13-15, 20-24, 29-33, 38-39 and 44-65 are presented for examination.

Applicant's Amendment filed October 23, 2008 and Supplemental Amendment filed November 14, 2008 have each been received and entered into the present application.

Claims 1-2, 13-15, 20-24, 29-33, 38-39 and 44-65 remain pending. Claims 1-2, 13-15, 20-24, 29-33 and 38-39 remain under examination. Claims 44-65 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 42-43 are cancelled. Claims 1 and 32-33 are amended.

Applicant's arguments, filed October 23, 2008 and November 14, 2008, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement, New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 13-15, 20-24, 29-33 and 38-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claim 1 reads upon a pharmaceutical composition comprising a therapeutically effective amount of a drug; a solubilizer selected from the group consisting of polyoxyl 40 castor oil, polyoxyl 35 castor oil, etc. (claim 1, l.3-12); and a release modulator which synchronizes the release of the drug, wherein the release modulator is selected from the group consisting of methylcellulose, a

hydroxypropylmethylcellulose, etc. (claim 1, l.14-20), wherein the composition is formulated to release the drug over an extended period of time, said extended period of time being between 2 and 24 hours, and wherein less than 50% of the drug is released within the first two hours.

Present claim 32 is directed to substantially identical subject matter as present claim 1, but for the fact that it is specifically directed to an oral dosage form thereof.

Present claim 33 is also directed to substantially identical subject matter as present claim 1, but for the fact that it is specifically directed to a solid oral dosage form thereof.

In particular, the specification and claims as originally filed fail to provide adequate written description for the newly added limitation directed to "wherein less than 50% of the drug is released within the first two hours" (claims 1 and 32-33).

MPEP §2163 states, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))…Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in

possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Applicant relies upon Figures 2, 4-5 and 8-9 of the originally filed application, which each respectively correspond to the formulations of Examples 2, 4, 6, 9 and 13. Example 2 is a formulation of cilostazol (125 mg), d-alpha-tocopherol polyethylene glycol succinate (572 mg), d-alpha tocopherol succinate (64 mg) and polyethylene glycol (52 mg). Figure 2, which corresponds to the release profile of the formulation of Example 2, demonstrates that slightly less than 40% of the cilostazol is released within the first two hours. Example 4 is directed to four formulations, one which contains cilostazol, d-alpha tocopherol polyethylene glycol 1000 succinate and polyethylene glycol 8000 and three which contain cilostazol, d-alpha tocopherol polyethylene glycol 1000 succinate, d-alpha tocopherol succinate and polyethylene glycol 8000. Example 6 is directed to two formulations: (1) Formulation 6-1, which comprises cilostazol (25 mg), CREMOPHOR RH40 (125 mg), HPMC K4M (85 mg), talc (9 mg), colloidal SiO_2 (1 mg) and polyvinylpyrrolidone K90 (45 mg); and (2) Formulation 6-2, which comprises cilostazol (25 mg), CREMOPHOR RH40 (125 mg), HPMC K4M (85 mg), talc (9 mg), colloidal SiO_2 (1 mg), polyvinylpyrrolidone K90 (45 mg), and sodium dodecyl sulfate (2.5 mg). Figure 4, which corresponds to the release profile of the formulations of Example 6, demonstrates that slightly less than 25% of the cilostazol is released within the first two hours using Formulation 6-1 and slightly more than 25% of the cilostazol is released within the first two hours using Formulation 6-2. Example 9 is also directed to two formulations: (1) Formulation 9-1, which comprises carvedilol (25 mg), d-alpha tocopherol polyethylene glycol 1000 succinate (221 mg), glycerol dibehenate (55 mg), HPMC K100LV (59 mg), HPMC K4MP (59 mg) and amorphous silica (1 mg); and (2) Formulation 9-2, which comprises carvedilol (25 mg), d-alpha tocopherol polyethylene glycol 1000 succinate (210 mg), glycerol dibehenate (53 mg), HPMC K4MP (56 mg), carbopol 940 (56 mg) and amorphous silica (1 mg). Figure 5, which corresponds to the release profile of the formulations of Example 9, demonstrates that less than 20%

carvedilol was released within the first two hours. Figures 8 and 9 correspond to formulations of Example 12, wherein formulation 12-1, 12-2, 12-3, 12-4 and 12-8 were studied, but only formulations 12-2, 12-3 and 12-4 demonstrated less than 50% release of the active agent over the first two hours. Notably, formulations 12-1 and 12-8 showed more than 50% drug release over the first two hours.

While such formulations, testing and results have been fully and carefully considered, the compositions of Examples 2, 4, 6, 9 and 13 are directed to very specific mixtures of drug(s) and release modulator/solubilizer combinations in particular amounts [e.g., Example 2 is 125 mg cilostazol, 572 mg d-alpha-tocopherol polyethylene glycol succinate, 64 mg d-alpha tocopherol succinate and 52 mg polyethylene glycol; and Example 6-1 is 25 mg cilostazol, 125 mg CREMOPHOR RH40, 85 mg HPMC K4M, 9 mg talc, 1 mg colloidal SiO_2 and 45 mg polyvinylpyrrolidone K90; and Example 6-2 is 25 mg cilostazol, 125 mg CREMOPHOR RH40, 85 mg HPMC K4M, 9 mg talc, 1 mg colloidal SiO_2, 45 mg polyvinylpyrrolidone K90, and 2.5 mg sodium dodecyl sulfate], whereas the instant claims are significantly broader in scope regarding possible drugs, release modulator/solubilizers and combinations thereof, as well as amounts of each component (note that, e.g., instant claim 1 provides no limitation on the amounts of each relevant component). Such disclosure of these very specific formulations, coupled with the fact that not all formulations falling within the scope of the instant claims did actually demonstrate less than 50% release of the drug over the first two hours (please reference, e.g., formulations 12-1 and 12-8) fails to be supportive of the concept that less than 50% drug is released within the first two hours from the composition using *any* drug, *any* claimed release modulator and/or *any* solubilizer component and/or *any* %w/w of drug, release modulator and/or solubilizer. The determination of less than 50% release of drug within the first two hours for particular exemplary embodiments of the invention fails to provide adequate written support to now narrow the claims to read upon the same degree of drug release when the composition does not comprise the same drug, the same release modulators and/or the same solubilizers in the same amounts and proportions as those specifically used in the exemplary

embodiments that did, in fact, generate drug release in the manner now claimed (i.e., less than 50% drug release over the first two hours). This newly added limitation represents a narrowing of the subject matter both claimed and disclosed in the specification and claims as originally filed that is not adequately supported, either explicitly or implicitly, by the original disclosure and clearly is a concept that was not in Applicant's possession at the time of the invention.

Furthermore, this disclosure found in the specification and claims as originally filed also fails to support the concept of "less than 50%" drug release. The compositions of the exemplary embodiments upon which Applicant relies to support his newly added limitation directed to "less than 50%" drug release each release a very specific percentage amount of cilostazol within the first two hours. For example, in Example 2, the cilostazol release is slightly less than 40%, and in Example 6, for formulation 6-1, the cilostazol release is slightly less than 25%, and for formulation 6-2, the cilostazol release is slightly more than 25%. Thus, the drug release demonstrated with the exemplary compositions does not cover the full range of 50% or less cilostazol release as now instantly claimed and, therefore, represents a broadening of the subject matter both claimed and disclosed in the specification and claims as originally filed that is not adequately supported, either explicitly or implicitly, by the original disclosure and clearly is a concept that was not in Applicant's possession at the time of the invention.

As stated in MPEP §2163, "The subject matter of the claim need not be described literally (i.e., using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement." However, considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of "wherein less than 50% of the drug is released within the first two hours" (claims 1 and 32-33).

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102 (New Grounds of Rejection)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 13-15, 20-24, 29, 32-33 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Amselem (U.S. Patent No. 5,891,469; 1999).

Applicant is notified that the Amselem reference applies under 102(b) against the presently claimed subject matter because the instant claims are not entitled to the effective filing date of U.S. Patent Application No. 09/447,690 (November 23, 1999). Specifically, the disclosure of the '690 application fails to provide adequate written description and/or enabling direction as to the synchronized release property of the drug and the solubilizer of the composition as claimed and, therefore, fails to satisfy the conditions necessary to entitle Applicant to such a date as the effective filing date of the instant application.

Amselem teaches pharmaceutical compositions capable of increasing the oral bioavailability of a lipophilic substance (col.5, l.40-50), comprising: (1) a lipophilic substance that possesses low water solubility and poor oral bioavailability (col.1, l.21-22), such as lipophilic substances that have a water solubility of less than 50 μg/ml (col.5, l.43-47), e.g., cannabinoids (col.5, l.44), which have aqueous solubility of a few micrograms or less (i.e., meets Applicant's limitation directed to solubility of 25 μg/ml or less as stated in claim 15), (2) the surfactant alpha-tocopherol polyethylene glycol succinate, usually with a mean molecular weight of 1000 (col.5, l.49-66), and further (3) at least one dispersion adjuvant, such as tocopherol acetate, polyvinylpyrrolidone, a medium or long chain triglyceride and/or polyethylene glycol (col.6, l.23-26 and col.6, l.58-66). Amselem also teaches that the disclosed composition may be administered in a therapeutically effective amount to a mammal in need of such a substance (see claim

19; col.14), wherein the substance may be in a gelatin capsule or tablet unit dosage form (see claims 9-10; col.14) and may also comprise any suitable nontoxic carrier or diluent powder or additive (col.7, l.4-15). Amselem further teaches that the lipophilic substance is present from 0.01-50% of the total solid weight of the composition, the surfactant TPGS is present from 5-65% of the total solid weight of the composition and the dispersion adjuvant is present from 5-75% of the total solid weight of the composition (col.6, l.37-57).

The teaching of tocopherol polyethyleneglycol (PEG) succinate, especially tocopherol polyethyleneglycol 1000 succinate, as the surfactant component of the disclosed pharmaceutical composition places the use of either the racemic or either enantiomeric form (d- or l-) of tocopherol PEG succinate clearly within the possession of the public. Furthermore, though Amselem does not expressly recognize the "release modulating" properties of the, e.g., tocopherol PEG succinate, tocopherol acetate, polyvinylpyrrolidone, or medium or long chain triglyceride, the very teaching of the identical chemical entity in overlapping amounts clearly indicates that whatever release modulating properties that Applicant has attributed to either of these compounds are necessarily present, absent factual evidence to the contrary, since chemical compounds cannot have mutually exclusive properties. Please reference MPEP §2112.01.

With regard to present claims 20-23, directed to the solubilizer increasing the solubility of the drug by at least 25% compared to the intrinsic aqueous solubility of the drug (claim 20) or the synchronized release of the drug and solubilizer with a correlation coefficient of greater than 0.80 or 0.90 or 0.95 (claims 21-23), such correlation values are, absent factual evidence to the contrary, present in the reference because Amselem teaches identical pharmaceutical formulations containing elements identical to, and capable of performing the same functions as, those elements presently claimed in the instant invention. In other words, the fact that Amselem teaches identical components in what, on its face, appears to be an identical configuration to that presently claimed, is clearly indicative of the fact that any

release characteristics attributed to such a composition would be necessarily present in the prior art of Amselem, absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990)).

Furthermore, with regard to the limitation of "wherein the aqueous solubility of the drug is dependent on pH" in present claim 29, such is not considered to further limit the composition of parent claim 1 because such a limitation fails to impart any physical or material property to the composition that is not already present in the claim from which it depends.

With regard to present claims 1 and 32-33, which now specify that the composition is formulated to release the cilostazol between 2 and 24 hours and wherein less than 50% of the drug is released within the first two hours, such properties are, absent factual evidence to the contrary, also present in the reference because Amselem teaches the formulation of the lipophilic drug with the surfactant and dispersion adjuvant compounds in clearly overlapping amounts and, thus, in the same ratios as presently claimed to product a composition that is substantially the same as that presently claimed. In other words, the fact that Amselem teaches identical components in identical, or at the very least, overlapping, amounts is clearly indicative of the fact that such release characteristics would be necessarily present in the prior art of Amselem, absent factual evidence to the contrary. Again, please see MPEP §2112.01.

Note, further, that Applicant has argued that Amselem only teaches more than 50% release of the active agent over the first two hours following administration (p.13-14, Remarks filed November 14, 2008) and, therefore, cannot be applied as pertinent prior art over the instantly claimed invention. This is

unpersuasive, since Amselem used very specific formulations of dexanabinol or coenzyme Q10, TPGS, and polyvinylpyrrolidone, also optionally with other dispersion adjuvants (see, e.g., Example 2) to measure the release of the active lipophilic ingredient over time as presented in the Figures of the reference. However, such formulations are exemplary embodiments of the disclosed invention of Amselem neither circumscribe the full scope of embodiments covered by the disclosure to Amselem nor limit the disclosure of Amselem to the activity and release shown with these exemplary compositions. In fact, Amselem encompasses a considerable scope of embodiments that comprise the same active agents in the same amounts as that instantly claimed wherein the release of the lipophilic ingredient was not specifically quantified and/or measured. However, in view of the fact that the pharmaceutical composition taught by Amselem comprises the identical active agents in identical amounts as presently claimed, the composition of Amselem must necessarily possess the same release characteristics when administered as that presently claimed whether recognized by the patentee or not because products of identical chemical composition cannot exert mutually exclusive properties when prepared or used in the same manner under the same circumstances. In other words, if the prior art teaches the identical chemical or physical structure of the composition (i.e., same active agents, same amounts, etc.), the properties that Applicant discloses and/or claims are necessarily present. Please reference MPEP §2112.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation, the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also

Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 13-15, 20-24, 29-33 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselem (U.S. Patent No., 5891,469; 1999) in view of The Merck Index (Eleventh Edition, Monograph 3924; 1989, p.624-625) and The Merck Index (Twelfth Edition, Monograph 504; 1996, p.84).

Amselem teaches pharmaceutical compositions capable of increasing the bioavailability of a lipophilic substance (col.5, l.40-50), comprising: (1) a lipophilic substance that possesses low water solubility and poor oral bioavailability (col.1, l.21-22), such as lipophilic substances that have a water

solubility of less than 50 μg/ml (col.5, l.43-47), e.g., cannabinoids (col.5, l.44), which have aqueous solubility of a few micrograms or less, (2) the surfactant alpha-tocopherol polyethylene glycol succinate, usually with a mean molecular weight of 1000 (col.5, l.49-66), and further (3) at least one dispersion adjuvant, such as tocopherol acetate, polyvinylpyrrolidone, a medium or long chain triglyceride and/or polyethylene glycol (col.6, l.23-26 and col.6, l.58-66). Amselem also teaches that the disclosed composition may be administered in a therapeutically effective amount to a mammal in need of such a substance (see claim 19; col.14), wherein the substance may be in a gelatin capsule or tablet unit dosage form (see claims 9-10; col.14) and may also comprise any suitable nontoxic carrier or diluent powder or additive (col.7, 4-15). Amselem further teaches that the lipophilic substance is present from 0.01-50% of the total solid weight of the composition, the surfactant TPGS is present from 5-65% of the total solid weight of the composition and the dispersion adjuvant is present from 5-75% of the total solid weight of the composition (col.6, l.35-57).

The teaching of tocopherol polyethyleneglycol (PEG) succinate in Amselem, especially tocopherol polyethyleneglycol 1000 succinate, as the surfactant component of the disclosed pharmaceutical composition places the use of either the racemic or either enantiomeric form (d- or l-) of tocopherol PEG succinate clearly within the possession of the public. Furthermore, though Amselem et al. does not expressly recognize the "release modulating" properties of the, e.g., tocopherol PEG succinate, tocopherol acetate, polyvinylpyrrolidone, or medium or long chain triglyceride, the very teaching of the identical chemical entity in overlapping amounts clearly indicates that whatever release modulating properties that Applicant has attributed to either of these compounds are necessarily present, absent factual evidence to the contrary, since chemical compounds cannot have mutually exclusive properties. Please reference MPEP §2112.01.

With regard to present claims 20-23, directed to the solubilizer increasing the solubility of the drug by at least 25% compared to the intrinsic aqueous solubility of the drug (claim 20) or the

synchronized release of the drug and solubilizer with a correlation coefficient of greater than 0.80 or 0.90 or 0.95 (claims 21-23), such correlation values are, absent factual evidence to the contrary, present in the reference because Amselem teaches identical pharmaceutical formulations containing elements identical to, and capable of performing the same functions as, those elements presently claimed in the instant invention. In other words, the fact that Amselem teaches identical components in what, on its face, appears to be an identical configuration to that presently claimed, is clearly indicative of the fact that any release characteristics attributed to such a composition would be necessarily present in the prior art of Amselem, absent factual evidence to the contrary. Please see MPEP §2112.01[R-3] ("Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ 2d 1655, 1658 (Fed. Cir. 1990)).

Furthermore, with regard to the limitation of "wherein the aqueous solubility of the drug is dependent on pH" in present claim 29, such is not considered to further limit the composition of parent claim 1 because such a limitation fails to impart any physical or material property to the composition that is not already present in the claim from which it depends.

Amselem fails to teach the specific therapeutic drugs instantly claimed (such as, *inter alia*, fenofibrate as in instant claim 2 or, *inter alia*, amiodarone as in instant claim 31) or the limitation "wherein the composition releases the drug over 2-24 hours and wherein less than 50% of the drug is released within the first two hours" (claims 1 and 32-33).

In view of the fact that Amselem teaches the disclosed pharmaceutical compositions for formulating any of a variety of lipophilic substances, i.e., those with low water solubility and poor oral

bioavailability, one of ordinary skill in the art at the time of the invention would have found it prima facie obvious to use such a delivery preparation for the formulation of other highly hydrophobic drugs (i.e., those with low water solubility and, thus, poor bioavailability), such as fenofibrate or amiodarone, because, as The Merck Index teaches, the antihyperlipoproteinemic agent fenofibrate was well known in the art to be practically insoluble in water (see Monograph 3924) and the antiarrhythmic agent amiodarone was well known in the art to be only very slightly soluble in water (see Monograph 504). Accordingly, in view of the extensive hydrophobicity of both the compounds taught by Amselem and fenofibrate and/or amiodarone, the skilled artisan would have had a reasonable expectation of success in effectively solubilizing fenofibrate and/or amiodarone in the delivery vehicle disclosed by Amselem because of the demonstrated success in effectively solubilizing the exemplary hydrophobic agents (i.e., dexanabinol, CoQ10, etc.) of the reference into such a formulation. Further, such a person would have been motivated to do so in order to enable effective dosing of fenofibrate and/or amiodarone with concomitant enhancement of resorption and bioavailability levels, reduced variability in resorption and bioavailability levels and also a concomitant reduction in the amount required to achieve effective dosing.

With regard to present claims 1 and 32-33, which now specify that the composition is formulated to release the drug between 2 and 24 hours and wherein less than 50% of the drug is released within the first two hours, such properties are, absent factual evidence to the contrary, also present in the reference because Amselem teaches the formulation of the lipophilic drug with the surfactant and dispersion adjuvant compounds in clearly overlapping amounts and, thus, in the same ratios as presently claimed to product a composition that is substantially the same as that presently claimed. In other words, the fact that Amselem teaches identical components in identical, or at the very least, overlapping, amounts is clearly indicative of the fact that such release characteristics would be necessarily present in the prior art of Amselem, absent factual evidence to the contrary. Again, please see MPEP §2112.01.

Note, further, that Applicant has argued that Amselem only teaches more than 50% release of the active agent over the first two hours following administration (p.14-17, Remarks filed November 14, 2008) and, therefore, cannot be applied as pertinent prior art over the instantly claimed invention. This is unpersuasive, since Amselem used very specific formulations of dexanabinol or coenzyme Q10, TPGS, and polyvinylpyrrolidone, also optionally with other dispersion adjuvants (see, e.g., Example 2) to measure the release of the active lipophilic ingredient over time as presented in the Figures of the reference. However, such formulations are exemplary embodiments of the disclosed invention of Amselem neither circumscribe the full scope of embodiments covered by the disclosure to Amselem nor limit the disclosure of Amselem to the activity and release shown with these exemplary compositions. In fact, Amselem encompasses a considerable scope of embodiments that comprise the same active agents in the same amounts as instantly claimed wherein the release of the lipophilic ingredient was not specifically quantified and/or measured. However, in view of the fact that the pharmaceutical composition taught by Amselem comprises the identical active agents as presently claimed in identical amounts to those presently claimed, the composition of Amselem must necessarily possess the same release characteristics when administered as that presently claimed whether recognized by the patentee or not because products of identical chemical composition cannot exert mutually exclusive properties when prepared or used in the same manner under the same circumstances. In other words, if the prior art teaches the identical chemical or physical structure of the composition (i.e., same active agents, same amounts, etc.), the properties that Applicant discloses and/or claims are necessarily present. Please reference MPEP §2112.

In re Best (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions and/or properties that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the Applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no

requirement that a person of ordinary skill in the art would have recognized the newly cited function and/or property at the time of invention, so long as the function and/or property can be demonstrated to be reasonably expected to be present. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Note that, even though *Toro* was decided in the context of inherent anticipation, considerations of inherent teachings arise both in the context of anticipation and obviousness (see, e.g., *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) or *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983) and MPEP §2112).

Claims 1-2, 13-15, 20-24, 29-33 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselem (U.S. Patent No. 5,891,469; 1999) in view of in view of The Merck Index (Eleventh Edition, Monograph 3924; 1989, p.624-625) and The Merck Index (Twelfth Edition, Monograph 504; 1996, p.84), and further in view of Banker (U.S. Patent No. 3,097,144; 1963).

Amselem, The Merck Index (Eleventh Edition) and The Merck Index (Twelfth Edition) as applied above.

Amselem fails to teach the specific use of a polyvinylpyrrolidone-vinyl acetate copolymer as the polyvinylpyrrolidone copolymer of the disclosed invention (claim 39).

Banker teaches heat-cured polymeric film coatings for medicinal compositions that contain polyvinylpyrrolidone copolymers (title), such as, e.g., a polyvinylpyrrolidone-vinyl acetate copolymer (col.2, 1.20-27), that impart protection from moisture, reduce wear and chipping during handling and

shipping an disguise unpleasant tastes (col. 1, 1.25-29) in solid medicinal dosage forms, such as tablets (col. 1, 1.23-25).

One of ordinary skill in the art would have found it prima facie obvious to apply the technique of coating the tablet formulation of Amselem with the heat-cured polymeric film coating containing, e.g., polyvinylpyrrolidone-vinyl acetate copolymer, to improve the tablet formulation for the predictable results of imparting protection from moisture, enhancing integrity of the tablet by reducing wear and chipping that would have reasonably occurred during handling and shipping of the tablet formulations and also to enhance the aesthetics and palatability of the tablet by, for example, disguising unpleasant tastes.

Conclusion

Rejection of claims 1-2, 13-15, 20-24, 29-33 and 38-39 is proper.

Claims 44-65 remain **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

February 12, 2009

/Ardin Marschel/
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